STATE OF CALIFORNIA

GEORGE DEUKMEJIAN, *Governor*

DEPARTMENT OF FOOD AND AGRICULTURE
1220 N Street
Sacramento, CA 95814

August 12, 1987

Ms. Jan Auerbach
Office of Pesticide Programs (TS-75-767)
U.S. Environmental Protection Agency
401 M Street, Southwest
Washington, D. C. 20460

Dear Ms. Auerbach:

Enclosed is the Abamectin Risk Characterization Document completed by the Division of Pest Management, California Department of Food and Agriculture.

As these documents are completed for active ingredients undergoing the risk assessment process, they will automatically be forwarded to you.

If you have any questions, please contact me.

Sincerely,

Rusty Millar

W. F. Millar
Registration Specialist
Pesticide Registration Branch
(916) 322-3564

Enclosures

7C>AVIDRSKA.KP

ABAMECTIN (AVID^{R})

RISK CHARACTERIZATION DOCUMENT

California Department of Food and Agriculture
Division of Pest Management, Environmental
Protection and Worker Safety
Medical Toxicology and Worker Health and Safety
Branches

May 15, 1987

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Abamectin (Avid^R)

Risk Assessment

SUMMARY

Abamectin (MK-936) is a naturally occurring microbial compound developed by Merck, Sharp and Dohme. It is the active ingredient in Avid^R 0.15EC, which is being proposed for registration in California as a miticide/insecticide to control leafminers and two-spotted spider mites on flower crops, foliage plants and other non-woody ornamentals in fields, shadehouses and greenhouses.

Abamectin has undergone a risk assessment because of adverse developmental effects reported in animal studies. The lowest reported NOEL is 0.05 mg/kg/day, based on maternal toxicity in CF_1 mice. Based on surrogate exposure studies in greenhouses, the highest estimated worker dermal exposure is 45.4 mg/day. Dermal absorption of abamectin is estimated to be approximately 1% of the exposure amount. Calculations of effective daily dosage and margins of safety indicate that full label protective requirements (i.e. rainsuit and respirator) may be necessary to achieve an acceptable safety margin for greenhouse workers. In order to achieve label compliance, it is recommended that Avid^R 0.15EC be registered in California for greenhouse/shadehouse applications only if a mandatory reporting system is implemented for all proposed uses.

INTRODUCTION

General Information

Abamectin (MK-936) is a miticide/insecticide developed by Merck, Sharp and Dohme. It is a macrocyclic lactone natural product from the soil microorganism, Streptomyces avermitilis, and consists of two biologically active homologous avermectin components containing a minimum of 80% avermectin B_1a and a maximum of 20% avermectin B_1b.(1) Abamectin acts by stimulating the release of gamma aminobutyric acid (GABA), an inhibitory neurotransmitter in arthropods and vertebrates.

Abamectin is the active ingredient (a.i.) in Avid^R 0.15EC, an emulsifiable concentrate containing 0.15 pounds of a.i. per gallon. Avid^R is currently registered by the United States Environmental Protection Agency (U.S. EPA) for application to field and greenhouse grown ornamental plants at a maximum rate of 0.02 pounds of a.i. per acre.

Abamectin is also registered by the U.S. EPA as a 0.011% [redacted] bait (Affirm^R) for use against imported red fire ants and is applied at a rate of 50 mg a.i. per acre on non-crop land.

There are currently no registered uses for abamectin on food crops although the registrant has a federal Experimental Use Permit (EUP) approved for testing against cotton mites (Agrimec^R) and a pending EUP for use on citrus (Agrimec^R). Agrimec^R [redacted] is to be applied a minimum of three times per season to cotton at 0.02 pounds a.i. per acre and to citrus at 0.025 pounds a.i. per acre. A temporary tolerance of 0.005 ppm (the analytical detection limit) has been approved by EPA for cotton; the temporary tolerance for citrus is pending EPA approval. Abamectin has also been tested on celery, lettuce, tomatoes, beans, peppers, potatoes, pears, apples, pecans, walnuts, almonds, tobacco and soybeans. The registrant intends to submit applications for permanent tolerances on vegetable crops in 1987.

California Registration

Abamectin, as Avid^R 0.15 EC, is currently being proposed for registration in California to control leafminers and two-spotted spider mites on flower crops, foliage plants and other non-woody ornamentals in fields, shadehouses and greenhouses.

The registrant has also indicated that they intend to submit applications in 1987 for full registration of abamectin for use on cotton and citrus in California. In addition, California has recently received and approved research authorizations using abamectin on lettuce, tomatoes and bell peppers, for the purpose of obtaining residue and efficacy data (2).

Based on registration activities at both Federal and State levels, and on the various experimental programs conducted with abamectin, the registrant appears to have intentions for promoting the use of abamectin on a wide variety of non-food and food crops. As the use of abamectin increases, it is anticipated that the risk assessment will be reviewed and updated to address any changes in potential human exposure.

Physical/Chemical Properties(1)

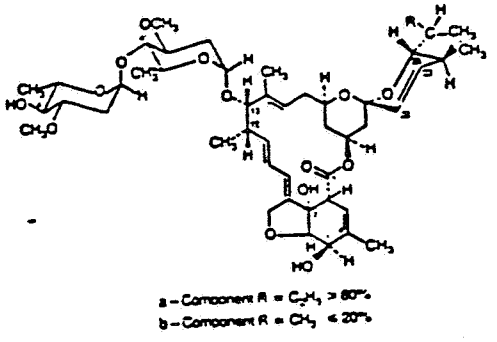
1. Chemical Name: Avermectin B_1
   - Avermectin B_1a (80%)
   - Avermectin B_1b (20%)

2. Common Name: Abamectin

3. Empirical Formula: Avermectin B_1a $C_{48}H_{72}O_{14}$

   Avermectin B_1b $C_{47}H_{70}O_{14}$

4. Chemical Structure:



a – Component R = C_2H_5 > 80%
b – Component R = CH_3 < 20%

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5.	Molecular Weight:	Avermectin B_1a: 873.11 Avermectin B_1b: 859.08
6.	Melting Point:	150-155°C
7.	Vapor Pressure:	1.5×10^{-9} mm Hg
8.	Solubility (21°C):	10 ug/L (water) 100 mg/ml (acetone) 350 mg/ml (toluene)

Basis for Risk Assessment

A risk assessment of potential health hazards from abamectin exposure has been conducted because of adverse developmental effects reported in animal studies. In a teratology study using CF_1 mice, a teratogenic effects (cleft palate) was reported at 0.4 mg/kg/day, with a no effect level (NOEL) of 0.2 mg/kg/day. The NOEL for fetotoxicity (lethality) was also 0.2 mg/kg/day. The lowest dosage producing maternal toxicity (tremors and lethality) was 0.075 mg/kg/day, with a NOEL of 0.05 mg/kg/day, which is the lowest NOEL reported for laboratory animals.

TOXICOLOGY PROFILE[a]

Acute Toxicity: Technical Material

1.	Acute Oral LD_{50} (rat):	8.7 mg/kg (male) 12.8 mg/kg (female)
2.	Acute Oral LD_{50} (mouse):	13.6 mg/kg [redacted] 29.7 mg/kg (methyl cellulose)
3.	Acute Dermal LD_{50} (rabbit):	>2,120 mg/kg
4.	Eye Irritation (rabbit):	Slightly irritating (Category III)
5.	Dermal Irritation (rabbit):	Nonirritating

Acute Toxicity: Formulated Material (1.8% emulsifiable concentrate)

1.	Acute Oral LD_{50} (rat):	0.722 ml/kg (male/female) (0.650 g/kg)
2.	Acute Dermal LD_{50} (rabbit):	>2.23 ml/kg (male/female)

a. Toxicology Summary in Appendix A.

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3.	Acute Inhalation (LC_{50}) (rat):	1.062 mg/L (male/female)
4.	Eye Irritation (rabbit):	Slight to moderate irritation (Category III)
5.	Dermal Irritation (rabbit):	Slight irritation (Category III)
6.	Dermal Sensitization (guinea pig)	Negative

Subchronic Toxicity (1.8% emulsifiable concentrate)

Several multi-exposure dermal toxicity studies were performed in rabbits. The lowest NOEL for mortality and tremors was 125 mg/kg. Possible testicular degeneration was indicated; however, subsequent studies demonstrated that this effect was caused by the stress of restraint methods. No other potential adverse effects were indicated.

Reproduction

Three rat reproduction studies were performed. The most recent was a two litter, two generation feeding study using dose levels 0, 0.05, 0.12, or 0.40 mg/kg. The parental NOEL was greater than 0.40 mg/kg. The reproductive NOEL was 0.12 mg/kg for decreased pup survival, decreased weight gain, and retinal changes.

Chronic Toxicity

A one year chronic dog feeding study was performed using dose levels of 0, 0.25, 0.5, or 1.0 mg/kg. The NOEL for mydriasis was less than 0.25 mg/kg. The NOEL for decreased body weight gain and alterations of clinical chemistry was 0.25 mg/kg.

A combined chronic toxicity-oncogenicity feeding study in mice was performed using dose levels of 0, 2, 4, or 8 mg/kg. The NOEL for tremors and mortality was 2 mg/kg. Oncogenic effects were not found. A combined rat chronic toxicity-oncogenicity feeding study was performed using dose levels of 0, 0.75, 1.50, or 2.0 mg/kg. The NOEL for tremors was 1.5 mg/kg. Oncogenic effects were not found.

Neurotoxicity

Since abamectin is not an organophosphate, delayed neuropathy studies are not required for registration. However, several of the studies reported the development of tremors and, in some cases, the loss of righting ability. These effects would be expected from the putative property of Avermectin B_1 in enhancing GABA activity. When histological examinations were performed on neural tissue from animals exhibiting CNS toxicity, no morphological alterations were seen.

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Genotoxicity

Several genotoxicity studies were conducted in three areas: gene mutation, chromosome aberration, and DNA damage and repair. All of the studies were negative.

Metabolism

Rats were given oral doses of vehicle, 0.14 mg/kg, or 1.4 mg/kg of labelled Avermectin B_1a. One group also had a 14 day pretreatment of 0.14 mg/kg unlabelled Avermectin B_1a. Animals were killed at 1, 2, 4, or 7 days after dosing. There was 85 to 95% recovery in the feces, urine, and tissue, with 69 to 82% recovery in the urine and feces alone. Tissue levels were low by day 7 (4% of day 1 levels). The half-life for tissue elimination was 1 day. The parent Avermectin B_1a was 60-90% of the tissue activity at day 2. Fat showed the highest concentrations.

RISK ASSESSMENT

HAZARD IDENTIFICATION

Developmental Toxicity

A rat teratology study was performed using dose levels of 0, 0.4, 0.8, or 1.6, mg/kg. A pilot study was performed using several higher dose levels. The maternally toxic and fetotoxic NOEL's were both 1.6 mg/kg.

A rabbit teratology study was performed using dose levels of 0, 0.5, 1.0, or 2.0 mg/kg. The maternally toxic NOEL was 1.0 mg/kg for decreased body weight. The teratogenic NOEL was 1.0 mg/kg for skeletal malformations.

Several CF-1 mouse teratology studies were performed using the parent Avermectin B_1 and the 8,9 photoisomer. An upper limit of 20% of the 8,9 isomer is found in the total residue after spraying. Avermectin B_1 was given to mice at dose levels of 0, 0.1, 0.2, 0.4, or 0.8 mg/kg. The teratogenic NOEL for cleft palate was 0.2 mg/kg; however, maternal toxicity, indicated by tremors, was found at the lowest dose tested. (Table 1). A follow-up study was performed in pregnant mice, using dose levels of 0, 0.025, 0.05, 0.075, or 0.1 mg/kg (Table 2). The maternally toxic NOEL was found to be 0.05 mg/kg. In the studies using the 8,9 photoisomer, the maternally toxic NOEL was 0.10 mg/kg, and the teratogenic NOEL was 0.015 mg/kg for cleft palate and exencephaly. Since the photoisomer makes up, at most, 20% of the total residue, the NOEL of 0.05 for maternal toxicity in the Avermectin B_1 study is the lowest and is the value that is used for the purposes of risk assessment.

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Table 1

	Dosage (mg/kg)				
Effect	0[a]	0.1	0.2	0.4	0.8
Maternal Toxicity (Death)	0/20	1/20	0/20	3/20	2/20
Maternal Toxicity (Tremors)	NR[b]	+	NR[b]	+	-
Cleft Palate	1/1[c]	1/1[c]	0	4/2[c]	5/2[c]

a. Two groups of 20 control animals.
b. Not reported.
c. Number of litters.

Table 2

	Dosage (mg/kg)				
Effect	0	0.025	0.05	0.075	0.10
Tremors Associated with Death	0	0	0	1/20	1/20
Tremors	0	0	0	0	2/20

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Table 1

	Dosage (mg/kg)				
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Maternal Toxicity (Death)	0/20	1/20	0/20	3/20	2/20
Maternal Toxicity (Tremors)	NR[b]	+	NR[b]	+	-
Cleft Palate	1/1[c]	1/1[c]	0	4/2[c]	5/2[c]

a. Two groups of 20 control animals.
b. Not reported.
c. Number of litters.

Table 2

	Dosage (mg/kg)				
Effect	0	0.025	0.05	0.075	0.10
Tremors Associated with Death	0	0	0	1/20	1/20
Tremors	0	0	0	0	2/20

EXPOSURE ASSESSMENT[a]

Air Blast Application to Citrus

The estimated exposures for mixers, loaders and applicators are based on studies using abamectin conducted by the registrant (3)(4). Protective clothing included: long pants, long sleeve shirt and impermeable gloves. Personal hygiene practices, such as washing, were also followed.

1) Mixer/loader: 0.604 ug/min
   - Daily exposure is assumed to occur for 1 hour.
   - Daily exposure = 0.604 ug/min x 60 min/day
     = 36.2 ug/day.

2) Applicator: 0.414 ug/min
   - Daily exposure is assumed to occur for 8 hours.
   - Daily exposure = 0.414 ug/min x 480 min/day.
     = 199 ug/day.

3) Mixer/Loader/Applicator(same person)
   (Mixer/loader exposure plus applicator exposure)
   - Daily exposure: 235 ug/day.

It is anticipated that the actual field application of Avid^R would result in lower exposures when the pesticide is used according to label requirements, which include "a disposable full body pesticide applicator suit, rubber gloves, boots and mask or pesticide respirator".

Greenhouse and Shadehouse Use

Exposure of workers in greenhouses/shadehouses occurs from the application by handgun and from foliage contact at reentry. Application of Avid^R by handgunners is assumed to result in the maximum worker exposure. The possible exposures estimated below for Avid^R are based on calculations from greenhouse studies using "surrogate" chemicals. (5)

Surrogate Pesticide	Surrogate Dermal Exposure (mg/hr/person)	Avid[b] Dermal Exposure (mg/hr/person)
Chlorpyrifos	204	1.36
Fluvalinate	378	5.67
Ethazol	12	0.24
Dicofol	126	1.51

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a. Details in Appendix B.

b. Based on surrogate dermal exposure. Assumes that dermal exposure is proportional to rate of application for a given type of use.

$$\text{Avid}^R \text{ dermal exposure} = \frac{\text{surrogate dermal exposure} \times \text{Avid}^R \text{ application rate}}{\text{surrogate application rate}}$$

Avid^R application rate = 600 mg/hr.

Reentry Exposure

Use of Avid® will also expose workers to residues on foliage. Following the spraying of chrysanthemums in Encinitas, California, foliar residues were measured by the registrant. Avermectin B_1 and degradation products were maximal at 2-4 hours post-spraying. When twice the recommended rate was used, the foliar residue was 16 nanograms/cm^2, and it declined with a half-life of approximately 40 hours. Parent compounds and primary degradation products can be detected for up to three days. The water soluble degradation products have negligible acute toxicity (LD_{50} > 5000 mg/kg day, rat oral). Using the Zweig-Popendorf Factor (6) to estimate daily dermal exposure of workers, maximum avermectin B_1 exposure is 640 micrograms/person/day[a]. These levels are within possible exposure levels of the other worker classes discussed above.

RISK CHARACTERIZATION

Toxicology Data

1. Lowest NOEL = 0.05 mg/kg/day[b]
   = 50 ug/kg/day

2. Dermal absorption: < 1% (assume 1% for calculations) (8)

3. Human body weight: 54.8 kg (woman of child bearing age) (9)

Exposure Data

1. Airblast Application to Citrus

   a) Mixer/loader
      - Daily exposure: 36.2 ug/day
      - Daily effective dosage: 0.007 ug/kg/day.[c]

   b) Applicator
      - Daily exposure: 198.7 ug/day
      - Daily effective dosage: 0.036 ug/kg/day

   c) Mixer/loader/applicator (same person)
      - Daily exposure: 235 ug/day
      - Daily effective dosage: 0.043 ug/kg/day

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a. Daily dermal exposure = foliar residue x Zweig-Popendorf Factor
   = 0.016ug/cm^2 x 5000 cm^2/hr/person x 8 hr/day
   = 640 ug/day/person

b. Based on maternal toxicity in 10 day oral toxicity study using CF_1 mice (7)

c. Daily effective dosage = $\frac{\text{daily exposure x dermal absorption factor}}{\text{body weight}}$

Risk Characterization (Continued)

2. Greenhouse/Shadehouse Use

Handgun Applicator	Estimated Range of Avid Exposure Based on Surrogate Chemicals: Low Exposure (Ethazol)	High Exposure (Fluvalinate)
- Dermal Exposure (mg/hr)	0.24	5.67
- Daily Effective Dosage (ug/kg/day)[a] (no protection)[b]	0.35	8.3
- Daily Effective Dosage (ug/kg/day) (coveralls)[c]	0.18	4.2
- Daily Effective Dosage (ug/kg/day) (label protection)[d]	0.0018	0.042

3. Reentry Exposure

- Daily exposure: 640 ug/day
- Daily effective dosage: 0.12 ug/kg/day

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a) Assumes 8 hr/day

b) No clothing

c) Effective dosage reduced by 50%

d) Disposable full body pesticide applicator suit, rubber gloves, boots, mask or pesticide respirator. Effective dosage reduced to 1% of coverall exposure.

Risk Characterization (continued)

Margins of Safety

1. Margins of safety (MOS) are calculated from the ratio of the NOEL and estimated exposure (i.e., effective daily dosage) as follows:

   MOS = NOEL/effective daily dosage.

2. Airblast - Citrus[a]

	MOS
- Mixer/loader (1hr)	7,560
- Applicator (8hr)	1,389
- Mixer/loader/applicator	1,163

3. Greenhouse/Shadehouse

	MOS for Avid Based on Surrogate Chemical Exposure	
	Low Exposure (Ethazol)	High Exposure (Fluvalinate)
Handgun Applicator		
- No Protection	143	6
- Coveralls	277	12
- Label requirements	27,777	1,190

4. Reentry

   The calculated MOS for workers exposed to foliar residues of Avid[R] is 417.

a) Protection: long pants, long sleeve shirt, impermeable gloves.

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DISCUSSION

The quantitative estimates of safety for Avid are dependent on low rates of application, low dermal absorption, rapid elimination from the body, low foliar persistence and strict compliance with label requirements. In addition, there are other factors which should be considered when assessing the overall magnitude of teratogenic or general toxicological risk.

The lowest dosage producing maternal lethality in CF_1 mice was approximately one-fifth of the lowest teratogenic dosage. The NOEL for this maternal effect was 0.05 mg/kg/day, the lowest NOEL established for abamectin in laboratory animal studies, and the NOEL used as the basis for the risk assessment. Laboratory studies have demonstrated considerable quantitative variability in the response of animals to abamectin. The pregnant mouse (CF_1 strain) has been the most sensitive mammal treated with abamectin.

In pregnant CD Sprague Dawley rats given abamectin, the NOEL for maternotoxicity is approximately 32 times greater than in the CF_1 mouse.

(10). The NOEL reported for maternotoxicity in rabbits given abamectin is 20 times greater than in the CF_1 mouse (11).

A structural analog, ivermectin, has a similar toxicological profile as abamectin and also is characterized by this variability in species sensitivity. The pregnant mouse (CF_1 strain) is also the most sensitive mammal given ivermectin with a maternotoxic NOEL slightly greater (2 times) than for abamectin (12). Ivermectin has been used as an antiparasitic agent in veterinary medicine (13, 14) and is currently being evaluated as a treatment for Onchocera volvulus (Hookworm) in humans (15, 16, 17).

The results of an "Oral Toxicity and Plasma Level Study in Monkeys" demonstrated a similarity in clinical signs, as well as "no observable effect levels" (1 mg/kg) for abamectin and ivermectin (18). This study also indicated a possible qualitative difference in toxic response between primates and other test animals since tremors and convulsions were not observed in the monkeys at dosage levels up to 24 mg/kg. The predominant adverse effect was emesis, with mydriasis and sedation also occurring with increasing dose. It is also evident from this study that the monkey can tolerate acute doses of either abamectin or ivermectin which were lethal to other test animals, including the mouse, rat and dog.

Humans may be approximately 3-fold more sensitive than the rhesus monkey to ivermectin (and possibly abamectin), since the dose producing mydriasis and sedation (as well as emesis) in the monkey is 3-fold higher than the dose which produced similar signs in a 15 kg. child who accidentally ingested between 6.6 and 8.6 mg/kg of ivermectin. Tremors and convulsions were not produced in the child, and he (she) recovered completely from the intoxication. No toxicity atrributable to ivermectin has been reported thus far for humans treated for onchocercias with a single, therapeutic dose of 0.2 mg/kg (15,16).

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Abamectin has been used in Australia in the treatment of endo- and ectoparasites in cattle with no reported developmental or maternal toxicity (19).

The currently available data for abamectin and ivermectin indicate that the CF_1 mouse is the most sensitive species to toxicological insult and is probably a conservative animal model in the extrapolation of abamectin toxicity to humans.

CONCLUSIONS

When abamectin is applied to citrus using an air blast sprayer, the calculated margins of safety for the mixer, loader and applicator are all above 1,000 and appear to be sufficient to protect these workers based on exposure/absorption data and the underlying assumptions.

The parent compounds and primary degradation products can be detected on the foliage for up to 3 days, and the half-life of the residue is approximately 40 hours, indicating a fairly rapid degradation process. The MOS calculated for workers who might be exposed to foliage (e.g., chrysanthemums) residue shortly (2-4 hours) after spraying is approximately 400 and appears to be sufficient to protect these workers.

For the handgun applicator using Avid^R in the greenhouse, a range of margins of safety were presented because no one surrogate exposure study can be considered as better than the other. However, using the MOS calculated from the high (fluvalinate) exposure study, it is apparent that the only way an adequate MOS can be achieved for the handgun applicator in the greenhouse is to require full worker compliance with the protective requirements on the product label. In order to assure this compliance, it is recommended that the California registration of Avid^R 0.15 EC for the currently proposed greenhouse/shadehouse applications be approved only if a mandatory reporting system is implemented for all proposed uses.

REFERENCES

1. Merck, Sharp and Dohme, Technical Data Sheet for Avamectin, March 1985.

2. California Department of Food and Agriculture Research Authorizations - Pesticide #701020 January 14, 1987 and #702075 February 19, 1987.

3. Merk, Sharp and Dohme, Field Studies Assessing Exposure of Workers Who Apply Abamectin (MK-936) 0.15EC with Airblast Sprayers to Citrus Groves. California Department of Food and Agriculture Document #50406-047.

4. Merck, Sharp and Dohme, Quantitative Risk Assessment for Airblast Application of Abamectin to Citrus. California Department of Food and Agriculture Document #50406-048.

5. Stamper, J. H., and Nigg, H. N. (1986) Personal communication regarding greenhouse exposure data.

6. Zweig, G., Gao, R., Witt, J., Popendorf, W. and Bogen, K. (1984) J. Argric. Food Chem. 32, 1232.

7. Merck, Sharp and Dohme, C-076 B_1a Oral Teratogeneic Evaluation in Mice. C-076B_{1a} Ten Day Oral Toxicity Study in Pregnant Mice California Department of Food and Agriculture Document # 50406-009.

8. Merck, Sharp and Dohme - Dermal Penetration of Avermectin B_1a in the Monkey PS#1, California Department of Food and Agriculture Document 50406-038.

9. U.S. EPA (1985) Hazard Evaluation Division Standard Evaluation Procedure: Teratology Studies, pp 41-47.

10. Merck, Sharp and Dohme. Oral Range Finding Study in Pregnant Rats and Oral Teratogenic Study in Rats (TT #82-705-1, #82-705-0) 11/10/82. CDFA Document #50406-032.

11. Merck, Sharp and Dohme. Oral Range Finding Study in Pregnant Rabbits and Oral Teratogenic Study in Rabbits, 11/10/82. (TT #82-706-1, #82-706-0) CDFA Document #50406-032.

12. Merck, Sharp, and Dohme. Comparison of Ivermectin and Abamectin Toxicity Data. MS&D Presentation 1/15/85. CDFA Document #50406-058.

13. Campbell, W.C.; Fisher, M.H.; Stapley, E.O.; Albers-Schonberg, G.; Jacob, T.A. (1983). Ivermectin: A Potent New Antiparasitic Agent. Science 221:823-828.

14. Campbell, W.C.; Benz, G.W. (1984). Ivermectin: A Review of Efficacy and Safety. J. Vet. Pharmacol. Ther. 7, 1-16.

15. Green, B.M.; Taylor, H.R.; Capp, E., et al., (1985). Comparison of Ivermectin and Diethylcarbamazine in the Treatment of Onchocerciacis. N. Eng. J. Med. 313, 133-138.

REFERENCES -Continued

16. Awadzi, K.; Dadzie, K.Y.; et al., (1985). The Chemotherapy of Onchocerciasis X. An Assessment of Four Single Dose Treatment Regimes of MK-0933 (Ivermectin) in human Onchocerciasis. Am. Trop. Med. Parasitol. 79, 63-78.

17. Cupp, E.W.; Bernardo, M.J., et al (1986). The Effects of Ivermectin on Transmission of Onchocerca Volvulus Science 231, 740-742.

18. Merck, Sharp and Dohme. MK-0933 and MK-0936 Oral Toxicity and Plasma Level Study in Monkeys (TT #85-013-0). 12/6/85, CDFA Document #50406-037.

19. Merck, Sharp and Dohme. Summary of Adverse Reaction to Ivermectin and Abamectin Animal Health Products for 1986. 5/18/87.

APPENDIX A

TOXICOLOGY SUMMARY

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

AVERMECTIN B1

SB 950-XXX, Tolerance # 50406

March 16, 1987

I. DATA GAP STATUS

Combined (chronic + onco) rat: No data gap, no adverse effect

Chronic dog: No data gap, possible adverse effect

Combined (chronic + onco) mouse: No data gap, possible adverse effect (not onco)

Repro rat: No data gap, possible adverse effect

Terato rat: No data gap, no adverse effect

Terato rabbit: No data gap, no adverse effect

Terato mouse: No data gap, possible adverse effect

Gene mutation: No data gap, no adverse effect

Chromosome: No data gap, no adverse effect

DNA damage: No data gap, no adverse effect

Neurotox: Not required

Note, Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
File name 7C>50406AV.JG

II. TOXICOLOGY SUMMARY

Combined (Chronic/oncogenicity) Toxicity, Rat

** 013, 016-025; 46635, 46641-46650; TT#82-099-0, Merck, Sharp and Dohme Research Labs., 5-29-85, Abamectin (Avid), 89-91%; 0, 0, 0.75, 1.5, 2.0 (increased to 2.5 at week 11 and decreased to 2.0 at week 13) mg/kg, 65/sex/group, two control groups; few animals with tremors at >2.0 mg/kg, not a true "effect" level. NOEL = 1.5 mg/kg. Originally evaluated as unacceptable but upgradeable, TRH, 8-7-86. Additional data (056 # 052064) supplied and study considered acceptable. TRH, 1-7-87.

Chronic Toxicity, Dog

** 012 46634 Fifty three week dietary toxicity study in dogs, (5/23/84, Merck Sharp & Dohme Research Laboratories) . Abamectin (at least 89% avermectin B1a and avermectin B1b; MK-0936 identified as L-676,863-00V54); 0, 0.25, 0.50, 1.0 mg/kg/day by feeding to 6 males and 6 females per group for 52 weeks. No significant adverse effects. Acceptable. BKD, 8-7-86

010 46627 Eighteen week oral toxicity study in dogs (Merck Sharp & Dohme Research Laboratories) . Avermectin B1a, purity not indicated; 0, 0.25, 0.5, 2.0, 8.0 mg/kg/day by gavage to 3 males and 3 females per group for 17 to 17.5 weeks. Adverse effects: whole body muscular tremors, ataxia, mydriasis, ptyalism, tonic convulsions, emesis, body weight decreases, and among animals which died or were sacrificed prior to scheduled termination, hepatocellular vacuolation and gallbladder edema. NOEL = 0.25 mg/kg/day. Unacceptable, incomplete. Dose levels too high, high mortality, too few animals, no histopathology for vehicle control or low dose groups. BKD, 8-6-86.

Oncogenicity, Rat See combined chronic/onco above

Combined (Chronic/Oncogenicity), Mouse

** 026 - 031; ; Merck Sharp and Dohme Research Laboratories, 6-20-86, abamectin, 89.0 - 91.1%, 0, 0, 2, 4, & 8 mg/kg/day, 50/sex/group, 2 control groups plus 12/sex/group for 6 and 12 month sacrifices. Increased mortality at 4 and 8 mg/kg/day. NOEL = 2 mg/kg/day. Originally reviewed as unacceptable but upgradeable, JCC, 8-13-86. Additional data (056, #52069), supplied and study considered acceptable. JCC, 1-6-87.

Reproduction, Rat

009 46625 Rat Reproduction, Merck, Sharp and Dohme Research Laboratories, no date,, TT# 77-706-0; Avermectin B1a, lot P-20 (no purity stated); 1? females/group (2 control groups) were given 0, 0.5, 1.0, or 2.0 mg/kg by gavage for 15 days before start of mating; 2.0 mg/kg reduced to 1.5 mg/kg after 5 doses; maternal NOEL = 1.0 mg/kg; Repro NOEL < 0.5 mg/kg (pup weight and survival). Unacceptable and not upgradeable. JG, JAP 8-8-86.

009 46626 Rat Reproduction; Merck, Sharp and Dohme Research Laboratories, no date, TT #77-712-0; Avermectin B1a, lot 00P22, no purity stated, 12 females/group (2 control groups) were given 0, 0.1, 0.2, or 0.4 mg/kg/day by gavage 14 days before mating through day 21 post partum; maternal NOEL = 0.4 mg/kg (HDT); Repro NOEL = 0.1 mg/kg (spastic movements of pups); no histology, incomplete, unacceptable protocol. JG, JAP 8-8-86.

015 46639 Pilot Rat Reproduction; Merck, Sharp and Dohme Research Laboratories, TT #82-707-0, 1-6-84, Avermectin, 94%, 12 females/group were given 0, 0.15, 0.5, 1.5, or 5.0 mg/ml in drinking water for 15 days before mating through day 21 of lactation. Nominal maternal NOEL = 1.5mg/ml; nominal neonatal NOEL = 1.5 mg/ml (neonatal weight gain and mortality). JG 8-11-86.

** 014 46636 "Reproductive effects of MK 0936 administered orally by gavage to Crl:COBS CD (SD)BR rats for two generations (TT #82-901-0)". Argus Research Laboratories, 1984; Avermectin, no purity stated; 30/sex/group were given 0, 0.05, 0.12 or 0.40 mg/kg/day by oral gavage for 2 generations, 2 litters per generation. Parental NOEL > 0.4 mg/kg, Repro NOEL = 0.12 mg/kg (pup survival and weight). Originally reviewed as unacceptable, JG,8-12-86 and JAP, 8-25-86. Additional data supplied, (056 #052066 and 058 # 52590, 52591) and study now Acceptable. JG, 1-8-87, 2-26-87; JAP, 2-26-87.

Teratology. Rat

032 46657 "Exploratory Teratology Studies in the Rat, TT 77-701-0", Merck, Sharp and Dohme Research Laboratories, 4-21-82, Avermectin B1a (no purity stated), range-finding study, 20 females/group (2 controls) given 0, 0.8, 1.6 or 3.2 mg/kg/day by oral gavage on days 6 - 15; 3 deaths at the high dose, maternal NOEL = 1.6 mg/kg, Teratogenic NOEL not established since only control and high dose fetuses were examined for visceral and skeletal findings, External teratogenic NOEL = 1.6 mg/kg. JG 8-8-86, JAP 8-28-86.

** 032 46659 "I. Oral Range-finding Study in Pregnant Rats and Oral Teratogenic Study in Rats", TT #82-705-1, #82-705-0; Merck, Sharp and Dohme Research Laboratories, 11-10-82, Avermectin, 94%, Pilot study with 10/group at 0, 0.25, 0.5, 1.0, and 2.0 mg/kg by gavage days 6 - 17, 1 death at 2.0 mg/kg. Full Study with 25/group at 0, 0.4, 0.8, 1.6 mg/kg by oral gavage days 6 - 19; nominal maternal NOEL = 1.6 mg/kg, nominal terato/feto NOEL = 1.6 mg/kg/day. Originally reviewed as unacceptable but upgradeable, JG, 8-8-86 and JAP, 8-28-86. Additional data received (057 # 52070 and 058 # 52581) made study acceptable. JAP 2-26-87.

Teratology. Rabbit

032 46658 "Oral Range-finding Exploratory Teratology Studies of Avermectin B1a in the Rabbit TT 76-724, 77-702-0/1", Merck, Sharp and Dohme Research Laboratories, 4-21-82, Avermectin B1a (no purity stated, no lot number), Pilot at 0, 0.25, 0.5, 1.0, 2.0 and 4.0 mg/kg/day. Full study (2 studies with a combined total of 25/dose group, 2 control groups) given 0, 0.25, 0.5, or 1.0 mg/kg/day by gavage on days 7 - 16. Apparent maternal NOEL = 1.0 mg/kg, Apparent teratogenic NOEL = 1.0 mg/kg. Not acceptable. JG, 8-8-86, JAP, 8-28-86.

** 032 46660 "II. Oral range-finding Study in Pregnant Rabbits and Oral Teratogenic Study in Rabbits, TT #82-706-1, #82-706-0, Merck, Sharp and Dohme Research Laboratories, 11-10-82, Range-finding at 0, 0.5, 1.0, 2.0 or 3.0 mg/kg/day by gavage on days 6-18. Full study at 0, 0.5, 1.0, or 2.0 mg/kg/day by gavage on days 6-27. Maternal NOEL = 1.0 mg/kg/day, Teratogenic NOEL = 1 mg/kg/day. Originally reviewed as unacceptabale but upgradeable,JG, 8-8-86, JAP, 8-28-86. Additional data were supplied (057 # 52071 and 058 #52581) and the study is considered acceptable, JAP, 2-26-87.

Teratology, Mice CF-1

009 46622 "Oral Teratogenic Evaluation in Mice, TT #76-723-0/1/2/3", Merck Sharp and Dohme, no date given, Avermectin B1a and B2 (no purity given), 2 replicate studies, with 10 and 15 /group = 25 total. Given 0, 0.1, 0.2, 0.4, or 0.8 mg/kg/day by gavage on days 6 - 15, For B1a, Maternal NOEL < 0.1 mg/kg (mortality), Teratogenic NOEL = 0.2 mg/kg. For B2, Maternal NOEL < 0.1 mg/kg, Teratogenic NOEL = 0.1 mg/kg. Tremors at all doses, no repro effects noted. Cleft palate seen in fetuses. Range finding studies conducted to 8.0 mg/kg/day with tremors, coma and death as the signs of maternal toxicity. Initially reviewed as unacceptable; JG, 8-6-86, JAP, 8-28-86. Additional data submitted, 057, # 052072 (individual fetal observations and clinical observations). Analysis of dosing solutions was not performed. Study still not acceptable. JAP 1-12-87.

009 46623 "Oral Teratogenic Evaluation in Mice, TT #77-705-0", Merck, Sharp and Dohme (no date); Avermectin B_{1a} (no purity stated); 20/group (2x20 for controls) were given 0, 0.1, 0.2, 0.4 or 0.8 mg/kg days 6-15 by oral gavage; Maternal NOEL < 0.1 mg/kg (tremors); Terat NOEL = 0.2 mg/kg (cleft palate); upgradeable. Initially reviewed as unacceptable; JG, 8-6-86, JAP, 8-28-86. Additional data submitted, 057, # 052072 (individual fetal observations and clinical observations). Analysis of dosing solutions was not performed. Study still not acceptable. JAP 1-12-87.

009 46624 "Ten-day Oral Toxicity Study in Pregnant Mice, TT #77-717-1", Merck, Sharp and Dohme (no date); Avermectin B_{1a}, no purity stated; 20 per group given 0, 0.025, 0.050, 0.075 or 0.10 mg/kg by oral gavage days 6-15; low pregnancy rate; maternal NOEL = 0.050 mg/kg; no data on fetuses - no terat NOEL available due to lack of data; acceptable as a range finding study.

010 46630 "Ten-day Dietary Maternotoxicity Study in Mice, TT 83-705-1", Merck, Sharp, and Dohme, 1984; Avermectin -88% (Tritiated at > 98%), nominal 0, 0.1, 0.3, Or 0.6 mg/kg/day, days 6-15 in the diet; NOEL = 0.1 mg/kg/day (actually, 0.06 due to diet intake and content) acceptable as "subacute"

Teratology - Mouse CF-1

DELTA 8,9 ISOMER OF AVERMECTIN B1

036 46683 "8,9 Isomer of Avermectin B1 Maternotoxicity and Teratology studies, TT 84-722-0"; Merck, Sharp & Dohme 1-8-86; (8, 9-Avermectin B_{1a}, 99%, L-652,280-00N); 8-13 Females per group given 0, 1.5, 3.0, 6.25, 25.0, or 50 mg/kg/day, 6-15 of gestation; no survivors in ≥ 3 mg/kg; NOEL's not established; 24/83 fetuses in 4/7 litters had cleft palate in 1.5 mg/kg (adverse effect), 0 in control; originally reviewed as unacceptable. JG, 8-

8-86, JAP, 8-28-86. Additional data supplied, analysis of dosing solutions, 058 # 052592, and study now acceptable, JAP 3-13-87.

036 46684 "Oral Maternotoxicity Study in Mice TT 84-722-1; Merck Sharp and Dohme ; 1-8-86; (8,9 Isomer of avermectin B_{1a} 99%); 12 females per group were given 0, 0.05, 0.10, 0.50 or 1.0 mg/kg by oral gavage days 6 - 15 . Terato NOEL = 0.05mg/kg (Cleft Palate); maternal NOEL = 0.10 mg/kg; Originally reviewed as unacceptable (missing data, animal number). JG, 8-8-86, JAP, 8-28-86. Additional data received, 058 # 052592, analysis of dosing solutions and study now acceptable, JAP 3-13-87.

036 46685 "Oral Teratology Study in Mice TT 85-710-0"(Main Study); Merck Sharp and Dohme; 1-8-86; (Avermectin, 8, 9 isomer of B_1, 99%) 25 females per group were given 0, 0.015, 0.03 or 0.06 (nominal) mg/kg/day, day 6-15; by oral gavage; study to confirm NOEL values; maternal NOEL = 0.06 mg/kg, TRAT NOEL = 0.015 mg/kg (exencephaly); Initially reviewed as unacceptable but upgradeable. JG, 8-8-86, JAP, 8-28-86. Additional data received, analysis of dosing solutions, 058 # 052592, and study now acceptable. JAP 3-13-87.

036 46686 "Oral Teratology Study in mice TT 85-710-1:(Main Study); Merck Sharp and Dohme; 8-8-86; (Avermectin, 8, 9 isomer of B1, 99%); 25 females per group given 0, 0.015, 0.03, 0.1 or 0.5 mg/kg/day by oral gavage, days 6-15; maternal NOEL = 0.1 mg/kg (nominal), TRAT NOEL = 0.015 mg/kg (nominal); Initially reviewed as unacceptable but upgradeable. JG, 8-8-86, JAP, 8-28-86. Additional data received, 058 052592, analysis of dosing solutions, and study now acceptable. JAP 3-13-87.

** 058 052592 Analytical results for mouse teratology studies conducted with delta 8,9 isomer of Avermectin B1 (TT 84-722-0/1 and TT 85-710/1). This information is sufficient to upgrade the studies to acceptable.

057 052073 Merck Sharp and Dohme discussion of exencephaly and cleft palate in mice treated with delta 8,9 isomer of Avermectin B1. Selected journal articles. JAP 1-12-87 (no worksheet)

Mutagenicity Gene Mutation

009 46621; Salmonella; Merck Sharp and Dohme 1976; (Avermectin B_{1a} (no purity stated); ± rat liver activation - aroclor or phenobarbital-induced; lot 00P02 at 0, 1, 10, or 100 ug/plate, lot 00P08 at 0, 20, 200, or 2000 ug/plate; strains TA1537, TA92, TA98 and TA100; unacceptable and not upgradeable. JG 8-5-86.

033 46663; Salmonella Strains TA1535, TA1537, TA1538, TA98 and TA100; Merck Sharp & Dohme - 1982; (Avermectin, 94%); ± rat liver activation; 0, 100, 300, 1000, 3000 or 10,000 ug/plate in triplicate, 1 trial; ppt at 3000 and 10,000 ug/plate; no evidence of increased reversion rate. Incomplete (no individual plate counts); unacceptable (no repeat trial); not upgradeable. JG 8-1-86.

** 033 46664; Chinese hamster V79 cells; Merck Sharp and Dohme - 1983; 8-1-86; (Avermectin, 94%); ± S-9, rat liver, two trials; 0, 0.03, 0.04, 0.045; 0.05 mM + S-9; 0, 0.003, 0.004, 0.005 and 0.006 mM,-S9; no increase in mutation frequency to cytotoxic concentrations; acceptable. JG 8-1-86.

033 46667; Salmonella, 5 Strains; Merck Sharp & Dohme - 1986; (Avermectin, 89%); TA1535, TA1537, TA1538, TA98, TA100 - No activation; 0, 100, 300, 1000, 3000 or 10,000 ug/plate; no increased reversion rate; unacceptable and not upgradeable. JG 8-4-86.

** 033 46668; Salmonella, Merck Sharp & Dohme - 1986; (Avermectin, 94%); TA1535, TA1537, TA1538, TA98, and TA100 ± rat liver activation at 0, 3, 10, 30, 100, or 1000 ug/plate in triplicate; no evidence of increased reversion rate. Considered acceptable along with other studies in salmonella. JG 8-5-86.

Mutagenicity Chromosome

033 46666; Chromosome-in vivo mouse chromosomal aberrations; SRI-1983; (Avermectin, 94%); 0, 1.2, 4.0 or 12.0 mg/kg by oral gavage to 12 (control) or 8 (test group) male mice; sacrifice at 6, 24 or 48 hours; no evidence of increase in aberrations; pilot study included; unacceptable but upgradeable. JG 8-4-86.

** 033 46669 Chromosome; in vitro aberrations; Merck Sharp & Dohme-1986; (Avermectin, 94%); CHO-WBL cells; ± rat liver activation -beta-Naphthaflavone and phenobarbital induced; 0, 0.01, 0.015, and 0.02 mM scored at 10.5 and 24 hours -S9; 0, 0.005, 0.010, 0.015 or 0.02 at 10.5 hours +S9; 3 hour exposure; no evidence for increased aberrations to cytotoxic levels; acceptable. JG 8-5-86.

Mutagenicity DNA

** 033 46665; 844 MUTA-DNA; alkaline elution with rat hepatocytes; Merck Sharp & Dohme - 1983; (Avermectin); 4 in vitro trials at 0 to 0.6 mM; 1 in vivo trial in rats; at 10.6, 3.5, or 1.06 mg/kg/male rat by oral gavage; 3 hours exposure in both types; no increase in SS breaks without increased cytotoxicity in vitro; no effects in vivo; acceptable. JG 8-1-86.

Neurotoxicity

Not required.

7C>SRS50406.JAP

TO: Margaret Reiff, Registration Specialist
Pesticide Registration Branch

FROM: Judith Parker, Medical Toxicology 3/17/87

REVISED DATA PACKAGE SUMMARY AND RECOMMENDATION SHEET

Active ingredient: Avermectin B_1
Formulated product name: Avid 0.15 EC
Formulation (excluding inerts):
SB 950#: ID#: C28098N
EPA Reg#: 618-96
Document #'s: 50406-008,009,10,12,13,14,15,16-25,26-31,32,33,34, 35,36,37, and 58 EPA MRID#:
Company name: Merck and Company

SUMMARY: ("CDFA One-Liners" from each study worksheet, significant information not mentioned in worksheets, other pertinent information).

ACUTE STUDIES - Technical

	Toxicity Category
Acute Oral Toxicity LD_{50}	I
Acute Dermal Toxicity	III
Acute Inhalation Toxicity	No study received
Primary Eye Irritation	III
Primary Dermal Irritation	IV

Acute Oral Toxicity

008; #46614; Acute Oral - rats; Merck Sharp and Dohme Research Labs; 8-10-81; (Avermectin B_1 Techn. 91.4%); dose levels 6.67, 10.00, 15.00, 22.50, and 33.75 mg/kg; 10 animals/sex/dose; no treatment related changes; gross and microscopic changes were considered spontaneous findings; LD_{50} (male) = 8.7 mg/kg (C.I. 4.4-11.8) LD_{50} (female) = 12.8 mg/kg (C.I. 10.4-14.9); Category I; acceptable. JSB 7-30-86

Acute Dermal Toxicity

008; 46615; Acute Dermal - rabbits; Merck Sharp and Dohme Research Labs; 2-7-84; (MK-0936 Techn. 94.0%); dose level 2.12 g/kg; sixth day 9/10 animals lethargic, ataxia, abnormal head movements, tremors, bradypnea and disorientation; at termination all rabbits had a 21-37% weight loss from initial body weights; no mortalities; LD_{50} (M/F)>2.12 g/kg; Category III; acceptable. JSB 7-30-86

008; 46616; Acute Dermal - rabbits; Merck Sharp and Dohme Research Labs; 3-16-83; (MK-0936 Techn. Avermectin B_1, 91.4%); dose levels of 100, 200, 400, 800 and 1600 mg/kg; majority of surviving rabbits at all dose levels had 1-30% weight loss; on day 3, 7/8 rabbits of the 1600 mg/kg group exhibited signs of ataxia, occasional tremors and loss of righting reflex (1-2 rabbits in 200, 400, and 800 mg/kg dosage groups had similar signs at 4

to 11 days after treatment); no evidence of toxicity at doses less than 200 mg/kg and essentially nonirritating to the rabbit's skin; acceptable. JSB 7-30-86.

Acute Inhalation Toxicity - No study received.

Primary Eye Irritation Study

008; 46617; Eye Irritation - rabbits; Merck Sharp and Dohme Research Labs 8-11-81; (Avermectin B_1 Powder-Techn. Grade, Avermectin B_1 Formulation-L-676, 863-27U03, and vehicle formulation); dose level 0.1 ml; 3M/3F unwashed eyes; all eyes cleared by 48 hours; Category III; originally revived as unacceptable, JSB 7-31-86; submission of additional data, 056 #52041, makes study acceptable, 1-6-87 GTP.

Primary Dermal Irritation

008 46618; Dermal Irritation - Rabbits; Merck Sharp and Dohme Research Labs, 8-11-81; (Avermectin B_1 Powder-Techn., Formulated, and vehicle); dose levels 0.5g, 0.5ml, and 0.5ml, respectively; all animals had zero scores at 48 hours; Category IV; acceptable. JSB 8-1-86.

Skin Sensitization

008; 46619; Skin Sensitization-Guinea pigs maximization test; Merck Sharp & Dohme Research Labs, 4-15-83; (MK-0936, Technical, 94%, L-676,863-00V50); dose level for day zero intradermal, day 7 topical, and day 21 challenge topical; 0.5%, MK-0936, 1.0, 0.5; 5.0, DNCB, 5.0, 5.0; 0, control 0, 0.5; respectively; MK-0936 not a skin sensitizer under the conditions of this study; acceptable; positive control study 056 #052063 confirms sensitivity potential of DNCB. JSB 8-1-86; GTP 1-6-87.

ACUTE STUDIES - Formulation

	Toxicity Category
Acute Oral Toxicity LD_{50}	III
Acute Dermal Toxicity	III
Acute Inhalation Toxicity	III
Primary Eye Irritation	III
Primary Dermal Irritation	III

Acute Oral Toxicity

034; 46670; Acute Oral-rat; Merck Sharp and Dohme Research Labs, 12-21-82; (Citrus Spray Formulation, L-676,863-113M09); dose levels treated 0.25, 0.40, 0.64, 1.02, and 1.63 ml/kg, vehicle 20 ml/kg. Decreased activity, ataxia and tremors; LD_{50} 0.722 ml/kg (0.596-0.885 95% CI.); Category III; acceptable. JSB 8-5-86.

Acute Dermal Toxicity

034; 46671; Acute Dermal-rabbits; Merck Sharp and Dohme Research Labs, 8-16-83; (MK-0936 Citrus Spray Formulation, L-676, 863-113 M14); dose level 2.23 ml/kg; formulation-4/10 animals bradypnea and lethargy, 2/10 ataxia,

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tremors, and convulsions, one animal died after onset of these signs; LD_{50} (M/F) > 2.23 ml/kg; Category III; acceptable. JSB 8-7-86.

Acute Inhalation Toxicity

034; 46672; Acute Inhalation-rats; Hazleton Labs, 5-22-79; (L-676,863-01X01); dose level nominal concn. 5.73 mg/l; one hour LC_{50} study; no actual concn. given; no MMAD given; unacceptable but upgradeable. JSB 8-8-86.

034; 46673; Acute Inhalation-Rat; (MK-0936 EC, L-676,863-113M) Bio/Dynamics, 2-24-84; dose levels actual concn. 0.033, 0.43, 0.64, 0.72, 2.8, and 6.5 mg/l, 5 animals/sex/dose; neuromuscular impairment and notable tremors in the formulated group only; discoloration of lungs in all animals of Group I and II and numerous animals of group III, V, VI, IX, and XI; LC_{50} (M/F) 1.062 mg/l (0.742 to 1.521 95% C.I.); Category III; acceptable. JSB 8-6-86.

Primary Eye Irritation

008; 46617; Eye Irritation- rabbits; Merck Sharp and Dohme Research Labs, 8-11-81; (Avermectin $B_1$1 Powder-Techn. Grade, Avermectin B_1 Formulations L-676,865-27U03, and vehicle formulation); dose level 0.1 ml; originally reviewed as unacceptable, JSB, 7-31-86. Submission of additional data ,056 # 052067 (L 676,863-27U03, category II) and 052068 (L 677,706-00B02, category III) makes study acceptable 1-6-87 GTP.

034; 46674; Eye Irritation-rabbits; Merck Sharp & Dohme Research Labs, 12-6-82; (MK-0936 Citrus Spray Formulation, L-676, 863-113M09); dose levels 0.1 ml of vehicle control group 3M/3F (unwashed) and 0.1 ml of citrus formulation, 3M/3F (unwashed); slight irritation in 2 rabbits at 7 days (discharge); Category III; acceptable. JSB 8-11-86. Individual values in 056, # 52069.

Primary Dermal

008 46618; Dermal Irritation - Rabbits; Merck Sharp and Dohme Research Labs, 8-11-81; (Avermectin B_1 Powder-Techn., Formulated, and vehicle); dose levels 0.5g, 0.5ml, and 0.5ml, respectively; all animals had zero scores at 48 hours; Category IV; acceptable. JSB 8-1-86.

034; 46675; Skin Irritation-rabbits; Merck Sharp & Dohme Research Labs, 12-2-82; (MK-0936 Citrus Spray Formulation, L-676, 863-113M09); dose level 0.5ml for vehicle control (3M/3F) and 0.5ml Citrus Spray Formulation (3M/3F); Citrus Spray Formulation - 5/6 rabbits very slight erythema at 72 hours, unabraded site in one animal score of 4 for erythema for 7 days. eschar formation after 5 days and persisted up to 16 days; Category III; acceptable; JSB 8-11-86.

Dermal Sensitization The need for this study will be determined by the Worker, Health and Safety Branch.

ACUTE STUDIES - METABOLITES

036; #46682; 811-Acute Oral-mice (L-652,280-00N; 8, 9 Isomer of MK-0936); Merck Sharp and Dohme Research Labs, 4-9-86; (8, 9 Isomer of Avermectin B_1); dose levels 5, 10, 20, 40 and 80 mg/kg, 10 animals/sex/dose and 40

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ml/kg [redacted] (vehicle control); LD_{50} (M/F)>80 mg/kg; Category II; acceptable. JSB 8-13-86.

036; #46681; Acute Oral (Photodegradation of nonpolar and polar metabolites of MK-0936) - mouse; dose levels - polar: 1250, 2500, and 5000 mg/kg, nonpolar: 6, 12, 24, and 48 mg/kg; no treatment-related gross changes observed at necropsy; bradypnea and decreased activity in all animals of both treated groups; LD_{50} nonpolar (M/F) > 48 mg/kg, LD_{50} polar (M/F) > 5000 mg/kg; Category I and IV, respectively; acceptable. JSB, 8-13-86.

SUBCHRONIC/OTHER STUDIES

035; #46676; TT#83-066-0; Repeated 23-day dermal-rabbits; Merck Sharp and Dohme 10-13-83; (MK-0936 E.C. Formulation L-676,863-113M21); dose level 250, 500, and 1000 mg/kg E.C. formulation and 1000 mg/kg vehicle control; 19 treatment-related deaths in all formulation dose levels; many rabbits of all dose groups lost or failed to gain weight; decreased relative and absolute weights of the testes; all treated groups had degeneration of the seminiferous tubules (slight to marked) at the 15th dose or >; no NOEL; supplementary data. JSB 8-11-86.

035; #46677; TT#84-002-0; 24-day repeated dermal (occluded-unabraded) rabbits; (MK-0936, 0.15 lbs/gal E.C. formulation, L-676,863-113M); Merck Sharp and Dohme, 2-10-84; dose levels treated formulation - 250, 500, and 1000 mg/kg and vehicle control 1000 mg/kg and 125 mg/kg (NOEL group for previous study); relative and absolute liver weights of the 125 mg/kg 18-20% lower than all other groups; most rabbits of all groups lost 3-9% b.w.; testicular degeneration in all groups ranging from very slight to moderate; no NOEL set; supplementary data. JSB 8-15-86.

035; No record#; TT#84-045-0; 25-day subacute unoccluded dermal-rabbits; Merck Sharp & Dohme 6-8-84; (MK-0936 E.C. Formulations and Vehicle); dose levels - saline control-1.1 ml/kg; vehicle control - 31, 125, and 1000 mg/kg; formulation [redacted] - 31, 62.5, and 125 mg/kg; formulation-[redacted] - 250 mg/kg; mean testicular weights stat. sign-34% diff. in absolute weights - all treated groups including saline control (very slight to slight) testicular degeneration - caused by restraint stress and/or stress caused by dosage administration; supplementary data. JSB 8-18-86.

035; #46678; TT#83-2947; 9-day subacute dermal - rabbits; Merck Sharp and Dohme, no date; (0.15 lbs/gal E.C. Formulation-MK-0936); dose level 1.1 ml/kg unoccluded and occluded; toxicity > for unoccluded compared to occluded; plasma levels > (25-43%) unoccluded when compared to occluded group; possible explanations, [redacted] increased absorption of MK-0936 or formulation was held mostly in the gauze and not exposed to the skin; supplementary data. JSB 8-15-86.

035; #46680; Restraint Methods; effects of different methods of restraint on testicular morphology of rabbits (TT#84-088-0) Merck Sharp and Dohme 2-7-85; 6 different groups with or without restraint, with or without treatment; shaved or unshaven, collared; testicular degeneration seen in animals with depressed weight gain or lost weight; testicular degeneration could be due to weight loss secondary to restraint or be primarily related or a combination of factors. JSB 8-16-86.

037 46689 MK-0933 and MK-0936 Oral Toxicity and Plasma Level Study in Monkeys; 12-6-85; Avid (Abamectin; MK-0936); Merck Institute for Therapeutic Research; Single oral doses of 0.2 - 24.0 mg abamectin per kg body weight were given [redacted] to 2 male and 2 female monkeys. Doses were given in ascending order at 2 to 3 week intervals. Mydriasis was evaluated at 2, 4, and 24 hours after dosing, clinical signs were observed daily, and body weight measured weekly. In some cases, blood samples were taken 0.25 - 96 hrs post-dose. The minimum-detectable-effect dosage was 2 mg/kg (with a plasma level of 96 ng/ml @ 8 hr.) based on emesis in one of the four monkeys. A dosage of 6 mg/kg produced emesis in two monkeys, and 8 mg/kg produced emesis in all four monkeys. Very slight mydriasis was seen in one monkey at 6 mg/kg, and variable slight to moderate mydriasis was seen in all monkeys at a dosage of 8 mg/kg. Only following a dosage of 24 mg/kg was mydriasis marked and consistent, and at this dosage it was accompanied by sedation. The response to 24 mg/kg was roughly similar to the response of an accidentally poisoned child who ingested 6.6-8.6 mg/kg. Although plasma levels were not determined in the child, similar dosages produced a plasma level of 150 ng/ml in a monkey. This is not a guideline study, but provides useful supplementary information. JCC, 1-5-87.

METABOLISM STUDIES

Metabolism. Rat

50406-039; 46692; Metabolism Study-rats; Merck, Sharp and Dohme Labs; 2-1-84; Avermectin B-1 [$5^{3}H$] and [3,7,11,13,23-^{14}C]; 1.4 mg/kg and 0.14 mg/kg labeled; 0.14 mg/kg for 14 days, pretreatment groups, 3/sex/group per sacrifice interval (1, 2, 4 and 7 days); 85-95% recovery of dose in feces and urine in 7 days (and tissues, 69-82% in feces and urine only); tissue levels were low by day 7, though totals (day 1 + 2 + 4 + 7) were about 8% of dose (~10% was G.I. tract); acceptable with other metabolism study (rec. #46710). DMG, 8-25-86.

50406-040; 46710; Metabolism Study-rats; Avermectin B_1; Merck, Sharp and Dohme Labs, 5-15-86; 1.4 and 0.14 mg/kg, ^{3}H and/or ^{14}C-labeled, low dose to naive or 14-day pretreated rats; tissue elimination T1/2-1 day, slightly lower in males than females; parent AB_1 is 60-90% of activity through day 2; 24-OHMe-B_{1a} and B3"-DMe-B_{1a} were major metabolites. Fat tissue showed highest concentrations. < 4% of day 1 levels remaining by day 7 in any high dose group. Unacceptable by itself, acceptable with metabolism study (Rec. #46692). DMG, 8-25-86.

SB950-MANDATED HEALTH EFFECTS STUDIES

Combined (Chronic/oncogenicity) Toxicity. Rat

013, 016-025; 46635, 46641-46650; TT#82-099-0, Merck, Sharp and Dohme Research Labs. 5-29-85, Abamectin (Avid), 89-91%, 0, 0, 0.75, 1.5, 2.0 (increased to 2.5 at week 11 and decreased to 2.0 at week 13) mg/kg, 65/sex/group, two control groups; few animals with tremors at >2.0 mg/kg, not a true "effect" level. Originally evaluated as unacceptable but upgradeable, TRH, 8-7-86. Additional data (056 # 052064) supplied and study considered acceptable. TRH, 1-7-87.

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Chronic Toxicity, Dog

012 46634 Fifty three week dietary toxicity study in dogs, (5/23/84, Merck Sharp & Dohme Research Laboratories) . Abamectin (at least 89% avermectin B1a and avermectin B1b; MK-0936 identified as L-676,863-00V54). 0, 0.25, 0.50, 1.0 mg/kg/day by feeding to 6 males and 6 females per group for 52 weeks. No significant adverse effects. Acceptable. BKD, 8-7-86

010 46627 Eighteen week oral toxicity study in dogs (Merck Sharp & Dohme Research Laboratories) . Avermectin B1a, purity not indicated. 0, 0.25, 0.5, 2.0, 8.0 mg/kg/day by gavage to 3 males and 3 females per group for 17 to 17.5 weeks. Adverse effects: whole body muscular tremors, ataxia, mydriasis, ptyalism, tonic convulsions, emesis, body weight decreases, and among animals which died or were sacrificed prior to scheduled termination, hepatocellular vacuolation and gallbladder edema. NOEL = 0.25 mg/kg/day; Unacceptable, incomplete. Dose levels too high, high mortality, too few animals, no histopathology for vehicle control or low dose groups. BKD, 8-6-86

Oncogenicity, Rat See combined chronic/onco above

Combined (Chronic/Oncogenicity), Mouse

026 - 031; ; Merck Sharp and Dohme Research Laboratories, 6-20-86, abamectin, 89.0 - 91.1%, 0, 0, 2, 4, & 8 mg/kg/day, 50/sex/group, 2 control groups plus 12/sex/group for 6 and 12 month sacrifices. Increased mortality at 4 and 8 mg/kg/day. NOEL = 2 mg/kg/day. Originally reviewed as unacceptable but upgradeable, JCC, 8-13-86. Additional data (056, #52069),supplied and study considered acceptable. JCC, 1-6-87.

Reproduction, Rat

009 46625, Rat Reproduction, Merck, Sharp and Dohme Research Laboratories, no date,, TT# 77-706-0; Avermectin B1a, lot P-20 (no purity stated); 12 females/group (2 control groups) were given 0, 0.5, 1.0, or 2.0 mg/kg by gavage for 15 days before start of mating. 2.0 mg/kg reduced to 1.5 mg/kg after 5 doses; maternal NOEL = 1.0 mg/kg; Repro NOEL < 0.5 mg/kg (pup weight and survival). Unacceptable and not upgradeable. JG,JAP 8-8-86.

009 46626, Rat Reproduction; Merck, Sharp and Dohme Research Laboratories, no date, TT #77-712-0; Avermectin B1a, lot 00P22, no purity stated, 12 females/group (2 control groups) were given 0, 0.1, 0.2, or 0.4 mg/kg/day by gavage 14 days before mating through day 21 post partum; maternal NOEL = 0.4 mg/kg (HDT); Repro NOEL = 0.1 mg/kg (spastic movements of pups); no histology, incomplete, unacceptable protocol. JG,JAP 8-8-86.

015 46639 Pilot Rat Reproduction; Merck, Sharp and Dohme Research Laboratories, TT #82-707-0, 1-6-84, Avermectin, 94%, 12 females/group were given 0, 0.15, 0.5, 1.5, or 5.0 mg/ml in drinking water for 15 days before mating through day 21 of lactation. Nominal maternal NOEL = 1.5mg/ml; nominal neonatal NOEL = 1.5 mg/ml (neonatal weight gain and mortality). JG 8-11-86.

014 46636 "Reproductive effects of MK 0936 administered orally by gavage to Crl:COBS CD (SD)BR rats for two generations (TT #82-901-0)". Argus Research Laboratories, 1984; Avermectin, no purity stated; 30/sex/group were given 0, 0.05, 0.12 or 0.40 mg/kg/day by oral gavage for 2 generations, 2 litters per generation. Parental NOEL > 0.4 mg/kg, Repro NOEL = 0.12 mg/kg (pup survival and weight). Originally reviewed as unacceptable, JG,8-12-86 and JAP, 8-25-86. Additional data supplied, (056 #052066 and 058 # 52590, 52591) and study now Acceptable. JG, 1-8-87, 2-26-87; JAP, 2-26-87.

Teratology, Rat

032 46657 "Exploratory Teratology Studies in the Rat, TT 77-701-0", Merck, Sharp and Dohme Research Laboratories, 4-21-82, Avermectin B1a (no purity stated), range-finding study, 20 females/group (2 controls) given 0, 0.8, 1.6 or 3.2 mg/kg/day by oral gavage on days 6 - 15. 3 deaths at the high dose, maternal NOEL = 1.6 mg/kg, Teratogenic NOEL not established since only control and high dose fetuses were examined for visceral and skeletal findings, External teratogenic NOEL = 1.6 mg/kg. JG 8-8-86, JAP 8-28-86.

032 46659 "I. Oral Range-finding Study in Pregnant Rats and Oral Teratogenic Study in Rats", TT #82-705-1, #82-705-0; Merck, Sharp and Dohme Research Laboratories, 11-10-82, Avermectin, 94%, Pilot study with 10/group at 0, 0.25, 0.5, 1.0, and 2.0 mg/kg by gavage days 6 - 17, 1 death at 2.0 mg/kg. Full Study with 25/group at 0, 0.4, 0.8, 1.6 mg/kg by oral gavage days 6 - 19; nominal maternal NOEL = 1.6 mg/kg, nominal terato/feto NOEL = 1.6 mg/kg/day. Originally reviewed as unacceptable but upgradeable, JG, 8-8-86 and JAP, 8-28-86. Additional data received (057 # 52070 and 058 # 52581) made study acceptable. JAP 2-26-87.

Teratology, Rabbit

032 46658 "Oral Range-finding Exploratory Teratology Studies of Avermectin B1a in the Rabbit TT 76-724, 77-702-0/1", Merck, Sharp and Dohme Research Laboratories, 4-21-82, Avermectin B1a (no purity stated; no lot number), Pilot at 0, 0.25, 0.5, 1.0, 2.0 and 4.0 mg/kg/day. Full study (2 studies with a combined total of 25/dose group, 2 control groups) given 0, 0.25, 0.5, or 1.0 mg/kg/day by gavage on days 7 - 16. Apparent maternal NOEL = 1.0 mg/kg, Apparent teratogenic NOEL = 1.0 mg/kg. Not acceptable. JG, 8-8-86, JAP, 8-28-86.

032 46660 "II. Oral range-finding Study in Pregnant Rabbits and Oral Teratogenic Study in Rabbits, TT #82-706-1, #82-706-0, Merck, Sharp and Dohme Research Laboratories, 11-10-82, Range-finding at 0, 0.5, 1.0, 2.0 or 3.0 mg/kg/day by gavage on days 6-18. Full study at 0, 0.5, 1.0, or 2.0 mg/kg/day by gavage on days 6-27. Maternal NOEL = 1.0 mg/kg/day, Teratogenic NOEL = 1 mg/kg/day. Originally reviewed as unacceptabale but upgradeable,JG, 8-8-86, JAP, 8-28-86. Additional data were supplied (057 # 52071 and 058 #52581) and the study is considered acceptable, JAP, 2-26-87.

Teratology, Mice CF-1

009; 46622 "Oral Teratogenic Evaluation in Mice, TT #76-723-0/1/2/3", Merck Sharp and Dohme, no date given, Avermectin B1a and B2 (no purity given), 2 replicate studies, with 10 and 15 /group = 25 total. Given 0, 0.1, 0.2, 0.4, or 0.8 mg/kg/day by gavage on days 6 - 15, For B1a, Maternal NOEL < 0.1

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mg/kg (mortality), Teratogenic NOEL = 0.2 mg/kg. For B2, Maternal NOEL < 0.1 mg/kg, Teratogenic NOEL = 0.1 mg/kg. Tremors at all doses, no repro effects noted. Cleft palate seen in fetuses. Range finding studies conducted to 8.0 mg/kg/day with tremors, coma and death as the signs of maternal toxicity. Initially reviewed as unacceptable; JG, 8-6-86, JAP, 8-28-86. Additional data submitted, 057, # 052072 (individual fetal observations and clinical observations). Analysis of dosing solutions was not performed. Study still not acceptable. JAP 1-12-87.

009; 46623 "Oral Teratogenic Evaluation in Mice, TT #77-705-0", Merck, Sharp and Dohme (no date); Avermectin B_{1a} (no purity stated); 20/group (2x20 for controls) were given 0, 0.1, 0.2, 0.4 or 0.8 mg/kg days 6-15 by oral gavage; Maternal NOEL < 0.1 mg/kg (tremors); Terat NOEL = 0.2 mg/kg (cleft palate); upgradeable. Initially reviewed as unacceptable; JG, 8-6-86, JAP, 8-28-86. Additional data submitted, 057, # 052072(individual fetal observations and clinical observations). Analysis of dosing solutions was not performed. Study still not acceptable, JAP 1-12-87.

009; 46624 "Ten-day Oral Toxicity Study in Pregnant Mice, TT #77-717-1", Merck, Sharp and Dohme (no date); Avermectin B_{1a}, no purity stated; 20 per group given 0, 0.025, 0.050, 0.075 or 0.10 mg/kg by oral gavage days 6-15; low pregnancy rate; maternal NOEL = 0.050 mg/kg; no data on fetuses - no terat NOEL available due to lack of data; acceptable as a range finding study.

010; 46630 "Ten-day Dietary Maternotoxicity Study in Mice, TT 83-705-1", Merck, Sharp, and Dohme, 1984; Avermectin -88% (Tritiated at > 98%), nominal 0, 0.1, 0.3, Or 0.6 mg/kg/day, days 6-15 in the diet; NOEL = 0.1 mg/kg/day (actually, 0.06 due to diet intake and content) acceptable as "subacute".

Teratology - Mouse CF-1

DELTA 8,9 ISOMER OF AVERMECTIN B1

036; 46683; "8,9 Isomer of Avermectin B1 Maternotoxicity and Teratology studies, TT 84-722-0"; Merck, Sharp & Dohme 1-8-86; (8, 9-Avermectin B_{1a}, 99%, L-652,280-00N); 8-13 Females per group given 0, 1.5, 3.0, 6.25, 25.0, or 50 mg/kg/day, 6-15 of gestation; no survivors in $\geq$ 3 mg/kg; NOEL's not established; 24/83 fetuses in 4/7 litters had cleft palate in 1.5 mg/kg (adverse effect), 0 in control; originally reviewed as unacceptable. JG, 8-8-86, JAP, 8-28-86. Additional data supplied, analysis of dosing solutions, 058 # 052592, and study now acceptable, JAP 3-13-87.

036; 46684; "Oral Maternotoxicity Study in Mice TT 84-722-1; Merck Sharp and Dohme ; 1-8-86; (8,9 Isomer of avermectin B_{1a} 99%); 12 females per group were given 0, 0.05, 0.10, 0.50 or 1.0 mg/kg by oral gavage days 6 - 15 . Terato NOEL = 0.05mg/kg (Cleft Palate); maternal NOEL = 0.10 mg/kg; Originally reviewed as unacceptable (missing data, animal number). JG, 8-8-86, JAP, 8-28-86. Additional data received, 058 # 052592, analysis of dosing solutions and study now acceptable, JAP 3-13-87.

036; 46685; "Oral Teratology Study in Mice TT 85-710-0"(Main Study); Merck Sharp and Dohme; 1-8-86; (Avermectin, 8, 9 isomer of B_1, 99%) 25 females per group were given 0, 0.015, 0.03 or 0.06 (nominal) mg/kg/day, day 6-15; by oral gavage; study to confirm NOEL values; maternal NOEL = 0.06 mg/kg, TRAT

NOEL = 0.015 mg/kg (exencephaly); Initially reviewed as unacceptable but upgradeable. JG, 8-8-86, JAP, 8-28-86. Additional data received, analysis of dosing solutions, 058 # 052592, and study now acceptable. JAP 3-13-87.

036; 46686; "Oral Teratology Study in mice TT 85-710-1:(Main Study); Merck Sharp and Dohme; 8-8-86; (Avermectin, 8, 9 isomer of B1, 99%); 25 females per group given 0, 0.015, 0.03, 0.1 or 0.5 mg/kg/day by oral gavage, days 6-15; maternal NOEL = 0.1 mg/kg (nominal), TRAT NOEL = 0.015 mg/kg (nominal); Initially reviewed as unacceptable but upgradeable. JG, 8-8-86, JAP, 8-28-86. Additional data received, 058 052592, analysis of dosing solutions, and study now acceptable. JAP 3-13-87.

058 052592 Analytical results for mouse teratology studies conducted with delta 8,9 isomer of Avermectin B1 (TT 84-722-0/1 and TT 85-710/1). This information is sufficient to upgrade the studies to acceptable.

057 052073 Merck Sharp and Dohme discussion of exencephaly and cleft palate in mice treated with delta 8,9 isomer of Avermectin B1. Selected journal articles. JAP 1-12-87 (no worksheet)

Mutagenicity Gene Mutation

009; 46621; Salmonella; Merck Sharp and Dohme 1976; (Avermectin B_{1a} (no purity stated); ± rat liver activation - aroclor or phenobarbital-induced; lot 00P02 at 0, 1, 10, or 100 ug/plate, lot 00P08 at 0, 20, 200, or 2000 ug/plate; strains TA1537, TA92, TA98 and TA100; unacceptable and not upgradeable. JG 8-5-86.

033; 46663; Salmonella Strains TA1535, TA1537, TA1538, TA98 and TA100; Merck Sharp & Dohme - 1982; (Avermectin, 94%); ± rat liver activation; 0, 100, 300, 1000, 3000 or 10,000 ug/plate in triplicate, 1 trial; ppt at 3000 and 10,000 ug/plate; no evidence of increased reversion rate. Incomplete (no individual plate counts); unacceptable (no repeat trial); not upgradeable. JG 8-1-86.

033; 46664; Chinese hamster V79 cells; Merck Sharp and ;Dohme - 1983; 8-1-86; (Avermectin, 94%); ± S-9, rat liver, two trials; 0, 0.03, 0.04, 0.045; 0.05 mM + S-9; 0, 0.003, 0.004, 0.005 and 0.006 mM,-S-9; no increase in mutation frequency to cytotoxic concentrations; acceptable. JG 8-1-86.

033; 46667; Salmonella, 5 Strains; Merck Sharp & Dohme - 1986; (Avermectin, 89%); TA1535, TA1537, TA1538, TA98, TA100-No activation; 0, 100, 300, 1000, 3000 or 10,000 ug/plate; no increased reversion rate; unacceptable and not upgradeable. JG 8-4-86.

033; 46668; Salmonella, Merck Sharp & Dohme - 1986; (Avermectin, 94%); TA1535, TA1537, TA1538, TA98, and TA100 ± rat liver activation at 0, 3, 10, 30, 100, or 1000 ug/plate in triplicate; no evidence of increased reversion rate. Considered acceptable along with other studies in salmonella.
JG 8-5-86.

Mutagenicity Chromosome

033; 46666; Chromosome-in vivo mouse chromosomal aberrations; SRI-1983; (Avermectin, 94%); 0, 1.2, 4.0 or 12.0 mg/kg oral gavage to 12 (control) or 8 (test group) male mice; sacrifice at 6, 24 or 48 hours; no evidence of increase in aberrations; pilot study included; unacceptable but upgradeable. JG 8-4-86.

033; 46669 Chromosome; in vitro aberrations; Merck Sharp & Dohme-1986; (Avermectin, 94%); CHO-WBL cells; ± rat liver activation -beta-Naphthaflavone and phenobarbital induced; 0, 0.01, 0.015, and 0.02 mM scored at 10.5 and 24 hours -S9; 0, 0.005, 0.010, 0.015 or 0.02 at 10.5 hours +S9; 3 hour exposure; no evidence for increased aberrations to cytotoxic levels; acceptable. JG 8-5-86.

Mutagenicity DNA

033; 46665; 844 MUTA-DNA; alkaline elution with rat hepatocytes; Merck Sharp & Dohme - 1983; (Avermectin); 4 in vitro trials at 0 to 0.6 mM; 1 in vivo trial in rats; at 10.6, 3.5, or 1.06 mg/kg/male rat by oral gavage; 3 hours exposure in both types; no increase in SS breaks without increased cytotoxicity in vitro; no effects in vivo; acceptable. JG 8-1-86.

CONCLUSIONS: Do data support registration? Yes, pending Risk Assessment determination of margin of safety.

YES Data support registration in the toxicity category ascribed.

RECOMMENDATIONS: In case of ongoing registration, register or do not register? What other specific studies or data requested?
REGISTER Pending Risk Assessment determination of margin of safety.

Jeffrey Berlin — 3-17-87

Associate Pesticide Review Scientist — **Date**

Judith A. Parker — 3-17-87

Judith A. Parker, Ph.D., D.A.B.T.
Toxicologist — **3-17-87 Date**

File; 7C SRS50406.JAP

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APPENDIX B

EXPOSURE ASSESSMENT

State of California

Memorandum

To : Larry Nelson, Chief
Medical Toxicology Branch

Via : Keith T. Maddy, Chief/Staff Toxicologist
Worker Health and Safety Branch

Date : May 6, 1987

Place : Sacramento

Phone: 5-8474

From : Department of Food and Agriculture - Robert I. Krieger, Staff Toxicologist
Worker Health and Safety Branch

Subject: Potential Human Avermectin B_1 Exposures
Product Name: Avid®
I.D. Number: C28098N
EPA Registration Number: 618-96
Company Name: Merck and Co., Inc.

On March 18, 1987, a memorandum from us summarized several potential human avermectin B_1 exposures.

Included among the calculations was an estimate of worker reentry exposure. It resulted from use of data from the spraying of chrysanthemums at twice the recommended rate. Two to four hours later the foliar residue was 0.016 ug/cm^2. The Zweig-Popendorf Factor (Zweig et al., Dermal Exposure to Carbaryl by Strawberry Harvesters, J. Agr. Food Chem. 32, 1232-1236, 1984) was used as an empirical factor to convert dislodgeable residue to potential daily dermal exposure. Discussion with Dr. Knaak and Dr. Leffingwell revealed a critical error in the Zweig et al. publication and the resulting work of the registrant.

The "Zweig-Popendorf Factor" was described loosely as a daily unit rather than as an hourly unit to derive an estimate of dermal exposure from dislodgeable residue data. In fact, the units of the empirical constant are cm^2/h.

Therefore, it was necessary to recalculate the estimated dermal exposure for persons working with avermectin B_1 treated plants. The estimated personal daily dermal exposure is:

$$0.016\ ug/cm^2 \times 5000\ cm^2/h/person \times 8\ h/day = 640\ micrograms/person/day$$

This will reduce the margin-of-safety, but not to unacceptable levels.

cc: Jim Knaak
Tom Leffingwell
Keith Pfeiffer

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SURNAME

SC-106

State of California

Memorandum

To : Larry Nelson, Chief
Medical Toxicology Branch

Via : Keith T. Maddy, Chief/Staff Toxicologist
Worker Health and Safety Branch

Date : March 18, 1987

Place : Sacramento

Phone : 445-8474

From : Department of Food and Agriculture - Robert I. Krieger, Staff Toxicologist
Worker Health and Safety Branch

Subject: Potential Human Avermectin B_1 Exposures
Product: Avid^R
I.D.# : C28098 N
EPA Reg # 618-96
Company: Merck and Co., Inc.

Avid^R Miticide/Insecticide is a 0.15 EC containing 2% avermectin B_1 (> 80% avermectin B_{1a}; < 20% avermectin B_{1b}). It is intended for <u>commercial use only</u> for control of leafminers and twospotted spider mites on flower crops, foliage plants and other non-woody ornamentals in fields, shadehouses and greenhouses.

<u>Acute Exposures</u>

The acute oral LD_{50}s for avermectin B_1 in rats and mice are 10 and 14 mg/kg. The product is a 2.0% emulsifiable concentrate with an oral LD_{50} of 0.7 ml/kg (>500 mg/kg). As a result the acute Toxicity Category for this product is III.

The acute dermal LD_{50} in rabbits is >1500 mg/kg which likewise results in a Toxicity Category III product classification. Additionally the product is non-sensitizing and non-irritating of either abraided or non-abraided skin (Toxicity Category IV). Avid^R is slightly irritating to the eye (Toxicity Category III). Effects are reversible within seven days.

Toxicity Category III also applies to the acute inhalation toxicity of avermectin B_1 (two studies provided).

The acute toxicities of concern (oral, dermal, inhalation) are classed as Toxicity Category III. The product label signal word is CAUTION.

<u>The precautions on the Avid^R label are adequate to protect workers from acute avermectin B_1 exposures.</u> As in all cases, compliance is a critically important issue. (The exact type of inhalation protection may require further clarification. At this point the use of a respirator is required by the label as a precautionary measure. The low vapor pressure, low rate of application, and low acute inhalation toxicity of the product (Toxicity Category III) suggest that the respirator may not be needed).

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SURNAME
SO-106 K. T. Maddy

Other Exposures

Avid^R Miticide/Insecticide is intended for use on shadehouse, greenhouse, and field-grown ornamentals. Its pesticidal activity as well as its human toxicity likely result from neurotoxicity related to GABA agonism (or antagonism). Avermectin B_1 neurotoxicity in susceptible organisms will result from excessive exposures. The effects should not be considered biologically unique or remarkable.

On the other hand, teratogenicity in mice (but not in rats or rabbits) is an unexpected toxicity which demands careful evaluation.

The following material in this section pertains to worker exposures related to proposed uses of Avid^R. The air blast application exposures are calculated from studies conducted by the registrant (50406-047) while greenhouse exposures used surrogate data (Stamper and Nigg, 1986).

Airblast Application To Citrus.

Following discussion with representatives of the Worker Health and Safety Branch, the exposures of mixer/loaders/applicators were determined by the registrant. They determined the level of worker exposure resulting from use of air blast equipment. That level will exceed the exposures of persons engaged in spraying of field ornamentals using boom sprayers.

$$\text{if EXPOSURE} = \frac{\text{ng avermectin}}{\text{min}} \times \frac{10^{-6}\text{mg}}{\text{ng}} \times \frac{60 \text{ min.}}{\text{hr}} \times \frac{1}{60 \text{ kg}}$$

$$= \text{mg avermectin/hr/kg body weight}$$

ABSORPTION is less than 1% of diluted or undiluted formulation

so EFFECTIVE EXPOSURE = 0.01 x (EXPOSURE) = dosage (absorbed dose)

Workers wearing long pants, long sleeve shirt, impermeable gloves, and personal hygiene were studied and exposure estimated.

$$\text{Mixer/Loader EXPOSURE} = \frac{604 \text{ ng}}{\text{min}} \times \frac{10^{-6}\text{mg}}{\text{ng}} \times \frac{1}{60 \text{ kg}} \times \frac{60 \text{ min}}{\text{hr}}$$

$$= 0.0006 \text{ mg avermectin/hr/kg body weight}$$

EFFECTIVE EXPOSURE = (0.01)(0.6 ug) = $\underline{0.006}$ ug/kg/hr.

According to usual use practices daily exposure is one hour

$$\text{Applicator EXPOSURE} = \frac{414 \text{ ng}}{\text{min}} \times \frac{10^{-6} \text{mg}}{\text{ng}} \times \frac{1}{60 \text{ kg}} \times \frac{60 \text{ min}}{\text{hr}}$$

$$= 0.0004 \text{ mg avermectin/hr/kg body weight}$$

$$\text{EFFECTIVE EXPOSURE} = (0.01)(0.0004) = 0.004 \text{ ug/hr}$$

According to usual use practices daily exposure is eight hours

The field application of Avid^R should result in substantially lower rates of exposure than indicated here since users will wear "a disposable full body pesticide applicator suit, rubber gloves, boots, and mask or pesticide respirator" rather than the more limited clothing worn by participants in this investigation. Thus, even lower levels of exposure would be expected when the product is used as directed.

Greenhouse and Shadehouse Use:

Worker exposure in greenhouses are related to application of Avid^R and foliage contact at reentry. Application by handgunners gives maximum exposure. The Federal registration of this product included estimates of greenhouse exposure based on work by Stamper and Nigg (1986). These data plus additional work were provided to the California Department of Food and Agriculture, Worker Health and Safety Branch.

Table 1. Chemicals Applied By Handgunners In Greenhouse

Pesticide	Formulation	Whole Body, No Clothing Exposure mg/hr	mg/hr/person
Chlorpyrifos	50% wp	700	204
		784	
		964	
Fluvalinate	22.3% EC	192	378
		444	
		1756	
		3652	
Ethazol	30% wp	12	12
		64	
		72	
Dicofol		504	126
Avid^R	0.15% EC		

The low concentration of avermectin B_1 in the product is the primary determinant of the low estimates of exposure which follow.

Table 2. Application Rates of Surrogate Chemicals and Avid^R

Pesticide	Kilograms/hr	Pounds/hr
Chlorpyrifos	0.09	0.20
Fluvalinate	0.04	0.08
Ethazol	0.03	0.07
Dicofol	0.05	0.10
Avid^R	0.0006	0.0013

Table 3. Maximum Potential Dermal Exposure and Effective Dermal Exposure

Pesticide	Spray Rate kg/hr	Dermal mg/hr/person	Surrogate Dermal as Avid[1] mg/hr/person	Effective 8-Hour[2] without protection mg/kg/day
Chlorpyrifos	0.09	204	1.36	2.0
Fluvalinate	0.04	378	5.67	8.3
Ethazol	0.03	12	0.24	0.35
Dicofol	0.05	126	1.51	2.2
Avid^R	0.0006			

Table 4. Estimated 8-Hour Avid[R] Exposures (mg/kg/day) Based Upon Surrogate Chemical Exposures

	Without Protection	Coveralls[3]	Label Protection[4]
Chlorpyrifos	2.0	1.0	0.01
Fluvalinate	8.3	4.2	0.042
Ethazol	0.35	0.18	0.0018
Dicofol	2.2	1.1	0.011

Calculation:

$$\text{Effective 8 hr. Dosage} = \frac{\text{Dermal exposure} \times \text{Dermal absorption} \times 8 \text{ hr.}}{54.8 \text{ kg}}$$

$$= \frac{\text{mg/hr/person} \times 0.01 \times 8 \text{ hr./day}}{54.8 \text{ kg/person}}$$

$$= \text{mg/kg/day}$$

[1] Calculation of Surrogate Dermal Exposures as Avid assumes that dermal exposure is proportional to rate of application for a given type of use.
Example: $\frac{204}{0.09} = \frac{x}{0.0006}$

[2] Estimated Avid exposure was converted to Effective 8-Hour Dermal assuming 54.8 kg person, 8 hour work period, and less than 1% dermal absorption.

[3] Overalls intercept at least 50% of the pesticde spray material (USEPA).

[4] Full body pesticide applicator suits reduce exposure to 1% or less of exposure of worker wearing coveralls (CDFA WH&S).

Reentry

Use of Avid^R will also expose workers to residues on foliage. Following the spraying of chrysanthemums in Encinitas, California, foliar residues were measured by the registrant. Avermectin B_1 and degradation products were maximal 2-4 hours after spraying. When twice (2x) the recommended rate was used, the foliar residue was 16 nanograms/cm^2 and it declined with a half-life of about 40 hours. Parent compounds and primary degradation products can be detected for up to three days. The water soluble degradation products have negligible acute toxicity (LD_{50} > 5000 mg/kg rat oral). Using the Zweig-Popendorf Factor to estimate daily dermal exposure of workers, maximum avermectin B_1 exposure is 80 nanograms/person/day (Dislodgeable x 5000 = Dermal; 0.016 ug/cm^2 x 5000 cm^2). These levels are well below possible exposure levels of the other worker classes listed above. Calculated MOSs will be above 1000.

Bystanders

Persons not wearing protective clothing are prohibited from areas where avermectin B_1 is being used.

Unintentional or unavoidable exposures due to environmental residues will be negligible due to low rates of application and rapid environmental breakdown.

Accidental Spills

Avid^R contain 2% avermectin B_1. Owing to the low extent of dermal absorption (<1%), very small amounts would be absorbed following accidental contact with unprotected skin. Due to small extent of absorption label instruction which call for washing with soap and water are adequate. Such exposure will not occur when label instructions are adhered to.

SUMMARY

Exposures of mixer/loader/applicators and persons reentering treated areas are sufficiently low to permit the safe use of avermectin B_1 miticide/insecticide. Quantitative estimates of safety depend upon low rates of application, low dermal absorption, rapid elimination from the body, and compliance with label requirements for full body pesticide applicator suit and other protective clothing. To assure compliance with label instructions, it may be desirable when we register Avid^R and to require manditory reporting of all proposed uses.

cc: Jim Wells
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